Receptor Interactions: Role of Pre- and Postsynaptic Nicotinic Receptors in Signal Transmission

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Since Langley first described in 1907 the existence of a "receptor substance" for nicotine in skeletal muscle that could mediate the effect of nicotine on muscle contraction, convincing evidence has been obtained that nicotinic acetylcholine receptors play an important role in synaptic transmission in the central nervous system and in the autonomic ganglia. It was recently shown that nicotinic receptors located on the somatodendritic or axon terminal region of the neuron represent a family of receptors different from those present on striatal muscle. Several subtypes of nicotinic receptors have been distinguished by pharmacological methods, receptor binding, and molecular biological techniques. In our recent study (Br. J. Pharmacol. 102:186-190, 1991) measuring norepinephrine release, the rank order of potency for presynaptic agonistic activity was DMPP = (-)nicotine > (+)nicotine >> cytisine, whereas in another study using binding techniques it was cytisine > (-)nicotine > DMPP > (+)nicotine. In binding studies it is not possible to precisely localize the receptors as in our release studies. It seems likely that nicotinic receptors localized pre- and postsynaptically are heterogeneous. Until now nicotine receptors have been postulated to be involved mostly in postsynaptic signalling responses. Recently, nicotine receptors localized on the axon terminals received significant attention in pharmacological studies and it was found that the release of different transmitters (dopamine, norepinephrine, acetylcholine, serotonin) is modulated by stimulation of these receptors. These actions of nicotine on its endogenous ligand, acetylcholine, are mediated via specific presynaptic nicotinic receptors, and result in an increase of release of several transmitters.

Cholinergic inputs, in both the central and the peripheral nervous systems, through stimulation of nicotinic receptors of pre- and postsynaptic localization are involved in different clinical symptoms. Stimulation of nicotinic receptors results in mood elevation, blood pressure increase, heart rate change, hormone release, and dopamine release in the limbic system and in the striatum (e.g., cigarette smoking

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Excitatory Amino Acid Receptors - Brian Meldrum

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Glutamate is the principal fast excitatory neurotransmitter in the brain. Aspartate and the sulfinic and sulfonic analogues of glutamate and aspartate may also be neurotransmitters. Glutamate acts on 4 receptor subtypes - the N-methyl-D-aspartate (or NMDA) receptor, the α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) receptor, the kainate receptor, and the metabotropic receptor. The first three open cation permeable channels, the metabotropic receptor acts via a G-protein to activate phospholipase C, converting phosphoinositides into diacylglycerol and IP_3 (which act as second messengers). Only the AMPA receptor has so far been purified, sequenced, cloned and expressed in Xenopus oocytes. In terms of pharmacology and physiology most is known about the NMDA receptors. It has 2 co-agonist sites,- at one glutamate (or NMDA) act, at the other glycine or D-serine act. 2 molecules of each appear to be required to open the ion channel. Thus there are 2 classes of competitive antagonist, NMDA site (e.g. AP7, CPP) and glycine site (5,7-dichloro- kynurenate, HA966). There are also non-competitive antagonists of the phencyclidine type (including ketamine and MK801) that act on the open ion channel. Antagonists that act selectively on AMPA and KA receptors have recently been described (NBQX, GYKI 52466).

The glutamatergic systems are involved in all major brain functions, sensory analysis, motor output and vegetative functions. They also play a part in synaptogenesis and in learning and memory.

They play a role in many disease processes. The phenomenon of excitotoxicity may be important in many acute and chronic neurodegenerative disorders. Excessive activation of any of the 3 main receptor subtypes can lead to sustained increases in $[Ca^{2+}]$, and to cell death. This is seen with exogenous excitotoxins such as domoic acid (producing limbic system lesions and amnesia) and ß-oxalylamino-L-alanine (producing neurolathyrism). Excitotoxicity also contributes importantly to acute cell death in stresses otherwise considered to be primarily metabolic in nature (status epilepticus, profound hypoglycaemia, cerebral ischaemia and trauma). It may play a role in chronic neurodegenerative disorders, such as motorneurone disease, Parkinsonism, Huntington's disease, olivopontocerebellar atrophy and senile dementia of the Alzheimer type.

Since 1980 a variety of drugs have been developed that selectively block the main glutamate receptors. Competitive and non-competitive antagonists acting at the NMDA receptor have been tested in a wide variety of preclinical models of neurologist disorder. They are effective in many different rodent and primate models of epilepsy and 2 competitive NMDA antagonists are about to enter clinical trial in epilepsy. Most interest has attached to the very powerful cerebroprotective effect of NMDA antagonists in animal models of stroke, a 30-60% reduction in cortical infarct volume is seen in models employing middle cerebral artery occlusion. Here also clinical trials are about to be initiated. Prospects are also good for trials in cerebral trauma. The chronic neurodegenerative disorders present a more severe challenge.

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has a protective effect in that those individuals who are or who have been smokers are less likely to develop idiopathic Parkinson's disease).

The knowledge of the heterogeneity of nicotinic receptors, their different localization, and their properties makes it possible to develop new compounds with selective activity and will enable us to selectively stimulate (nicotine receptor agonist) or inhibit (nicotine receptor antagonist) one of the effects of cholinergic activation, thereby enable us to selectively affect clinical symptoms.

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